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| EXAMINER | |
|---|---|
| RAMACHANDRAN, UMAMAHESWARI | |
| ART UNIT | PAPER NUMBER |
| 1627 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/729,056 | GRAINGER ET AL. | |
| | Examiner | Art Unit | |
| | UMAMAHESWARI RAMACHANDRAN | 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *,153-154, 157-165, 174-176, and 181-186* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *,153-154, 157-165, 174-176, and 181-186* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/23/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 2/23/2010. Claims 1-152, 155-156, 166-173, 177-180 have been canceled. Applicants have added claims 185 and 186. Claims 153, 154, 157-165, 174-176, 181-186 are pending and are being examined on the merits herein.

### Response to Remarks/Arguments

Applicants' state that as neither the present application nor the '775 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the '775 application. Accordingly, the ODP rejection is maintained and is given below for Applicants' convenience Applicants' arguments regarding the ODP rejections over patents 5,472,985 and 5,599,844 and 112(1) new matter rejection have been found to be persuasive and accordingly, the rejections are withdrawn. Applicants' arguments regarding the ODP rejections over 5,773,479, 5,847,007, 6,166,090 and 6,251,920, 112(1) enablement and 103(a) rejections have been fully considered and found not to be persuasive. Applicants' arguments have been addressed below. Applicants' addition of new claims necessitated the modified rejections presented in this office action. Accordingly, the action is made Final.

### Application Priority

This application, 10729056, filed 12/05/2003 is a continuation of 09754775, filed 01/04/2001, 09754775 is a continuation of 08973570, filed 12/05/1997 ,now U.S. Patent

#6197789, 08973570 is a national stage entry of PCT/US96/10211 , International Filing Date: 06/07/1996, PCT/US96/10211 is a continuation in part of 08478936, filed 06/07/1995 ,now abandoned, PCT/US96/10211 is a continuation in part of 08476735, filed 06/07/1995 ,now U.S. Patent #5595722, PCT/US96/10211 is a continuation in part of 08477393, filed 06/07/1995 ,now U.S. Patent #6395494 and having 2 RCE-type filings therein, PCT/US96/10211 is a continuation in part of 08486334, filed 06/07/1995 ,now U.S. Patent #5770609, 08486334 is a continuation in part of 08242161, filed 05/12/1994 ,now U.S. Patent #5847007 and having 1 RCE-type filing therein 08242161 is a continuation in part of 08061714, filed 05/13/1993 ,now abandoned. Applicants amendment of claims including the limitation “sustained release dosage form" subject matter is found in U.S. Patent 5.770.609. Accordingly, the priority for this subject matter ‘sustained release dosage is given as the filing date of the patent application, June 7 1995.

## ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 153, 154, 157-165, 169-175, 181, 182, 185, 186 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194,196-203, 205-211 and 231 of copending Application No. 09/754,775. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the method claimed in claims 153, 154, 157-165, 169-175 of the instant application utilizes the same biological pathway comprising increasing the level of TGF-beta encompassing utilizes the same active agents in the method of claim 173 of the co-pending application. The co-pending application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the application and hence renders obvious over the diseases and the agents claimed in the co-pending application. The co-pending application do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 153, 154, 159, 160, 165, 181-182, 185, 186 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 of U.S. Patent No. 5,773,479. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153, 154, 159, 160, 165, 181-182185, 186 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 9, 10, 11 of U.S. Patent No. 5,847,007. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The

patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153, 154, 159, 160, 165, 181-182185, 186 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10 of U.S. Patent No. 6,166,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153, 154, 159, 160, 165, 181-182, 185, 186 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 19, 27, 30-37, 38, 39, 41, 42 of U.S. Patent No. 6,251,920. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating a condition selected from atherosclerosis, stroke, thrombosis, myocardial infarction condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153, 154, 159, 160, 165, 181-182, 185, 186 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 6,262,079 Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of inhibiting vascular smooth muscle cell proliferation in a mammal comprising administering structural analogs of tamoxifen. The instant application is towards the method of inhibiting smooth muscle cells administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious

over the disease and the agents claimed in the patent. The patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153-154, 157-165, 169-186 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not teach administration of any of the claimed compounds in treating any of the cardiovascular indication in mammals as listed in the claims. The compounds claimed in treating cardiovascular indication have different biological activities, bioavailabilities, pharmacokinetic profiles, and pharmacological efficacy and does not reasonably provide enablement for a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter. The prior art as shown below in 'state of the art' section teaches the adverse role of tamoxifen in conditions like thrombosis, and stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

***(1) The Nature of the Invention:***

The rejected claims are drawn to a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that is a structural analog of tamoxifen (claims 153, 154, 157-165, 174-176, 181-184), a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid (181-184) b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit plaque (claims 153, 154, 157-165), inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof (claims 181-184).

***(5) Breadth of the Claims:***

The claims (181-84) are broad and embrace treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that is a structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof. The claims are broad with respect to the different agents claimed because there are a number of structural analogs of tamoxifen, stilbene antisteroids, 1, 2 diphenylethane antisteroids and naphthalene antisteroids known and yet to be discovered.

***(6)/(7) Guidance of the Specification and Working Examples***

The specification provides guidance and working examples related to: 1) impact of Tamoxifen on Vascular Smooth Muscle Cells and the Relationship thereof to TGF-Beta Production and Activation Cell culture, DNA synthesis assay and cell counting (2) heparin Effect on VSMC Proliferation and Differentiation (3) comparison of Enzyme-Dispersed and Explant-Derived Human VSMC (4) TGF-beta and Transgenic apo(a) Mice - used to study whether inhibition of TGF-beta activation, resulting in enhanced VSMC proliferation, represents a key step in atherogenesis (5) Tamoxifen Inhibits Migration and Lipid Uptake in VSMC in vitro and in Transgenic Mice (6) Effect of Idoxifene on Cultured Human VSMCs (7) Tamoxifen elevates TGF-.beta. and

suppresses diet-induced formation of lipid lesions in mouse aortae (8) Determination of Active and Acid Activatable TGF-.beta. in Human Sera, Platelets and Plasma by Enzyme-Linked Immunosorbent Assays (9) Association of TGF-beta with Lipoprotein Particles. However, there are no working examples and the specification does not teach administration of claimed agent(s) to a mammal in general or to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

***(2/4) State/Predictability of the Art:***

There is prior art teachings regarding lowering serum level cholesterol levels thereby treating or improving atherosclerotic conditions comprising administering to patients raloxifene (Black et al. U.S. 5,464,845), droloxifene (Fontana U.S. 5,426,123). The method of treating lipid accumulation, increase plaque stability comprising administering agents that include tamoxifen, tamoxifen analogs is predictable from the prior art. However, it is not predictable from the prior art that all known and yet to discover compounds of class, stibene antisteroids, naphthalene antisteroids etc will be useful in a method of treating a cardiovascular indication characterized by a decreased lumen diameter as there are teachings that relate to the side effects or toxic effects of drugs like hexesterol, clomiphene. Biofarma document (www.biofarma.kiev.ua\) teaches hexesterol's side effects include nausea, vomiting, vertigo and an administration of large/high doses cause toxic liver injury, excessive endometrium proliferation etc and the contraindications include diseases of the liver and kidney, malignant and benignant neoplasms in women under to , diseases connected with heightened level of blood

coagulation etc and there are drug interactions involved with other medicinal products such as progesterone, pregnin etc. The document regarding clomiphene (drugs.com, clomiphene citrate) teaches that patients with liver disease, have undiagnosed vaginal bleeding, endometriosis, ovarian cysts etc should not take clomiphene and further teach that the side effects include allergy reactions, ovarian hyperstimulation syndrome etc. Also, the prior art by Barath et al. (U.S. 5,242,397, filing date Jun 2 1992) teaches a method of treating a blood vessel that contains an atherosclerotic lesion by administration of an agent such as tamoxifen (col. 6, claims 1, 2). The prior art by Nakagawa et al. (Angiology, 1994, May 45, 5, 333-8) teaches a case of myocardial infarction, intracoronary thrombosis in two major arteries due to hormone therapy that included administration of 30 mg of tamoxifen. Dahan et al. in The Lancet, Mar 16 1985 teaches venous and arterial thrombosis in patients on tamoxifen therapy. Nevasaari in The Lancet, Oct 28, 1978 teaches that contraindications to the use of oestrogens included thromboembolic disorders and further states that four patients with metastatic breast cancer have had deep vein thromophelebilits while taking drug tamoxifen. Levine in P 406 (The NEJM, 1988, 404-407) states that Tamoxifen, an antiestrogenic agent has been reported to be associated with thromboembolism in patients with metastatic breast cancer. Also, the reference in the abstract teaches that chemotherapy contributes to thrombosis in patients with breast cancer. Also, Chlebowoski's teachings in Clin Breast Cancer, 2006, Feb 6, Suppl 2, S58-64 indicate that the clinical evidence suggests that tamoxifen increases stroke risk (see abstract). The reference teaches that women with breast cancer who were treated with tamoxifen had an 82% increased risk

of ischemic stroke and a 29% increased risk of any stroke and tamoxifen has been shown to consistently increase the risk of stroke in randomized clinical trials (p S 60, col. 2, lines 2-6). McDonald et al. (BMJ, 303, 24 Aug 1991) teaches that women receiving adjuvant tamoxifen found a significant reduction in the incidence of myocardial infarction (p 436, discussion, col.2, para 2). However Rutqvist in p 258 (Recent Results Cancer Res. , 1993, 257-66) (Other cardiovascular Effects, para 2) teaches that "In the Scottish Adjuvant Tamoxifen trial there was significant decreased incidence of myocardial infarction in patients in the tamoxifen group. However, other trials of similar size have not demonstrated such a benefit". It is not predictable from such prior art studies whether tamoxifen is useful in treating a cardiovascular indication such as stroke or thrombosis or myocardial infarction. Hence it is highly unpredictable to determine whether tamoxifen analogs would be useful in such diseases when tamoxifen a structurally agent has had either adverse effects (stroke, thrombosis) and mixed results (myocardial infarction) from the prior art and there is no data or studies provided in the specification to show that tamoxifen analogs would be useful in cardiovascular indications such as stroke or thrombosis or myocardial infarction.

**(8) The Quantity of Experimentation Necessary:**

In order to enable the instantly claimed methods that commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct experiments testing the compounds claimed for treating a cardiovascular indication. In order to practice the above claimed

invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system to test the composition in a method of treatment of cardiovascular indication. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Considering the side effects, drug interactions and contraindications of compounds like clomiphene, hexesterol in the prior art this would be an arduous and daunting task. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a cardiovascular indication administering structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid in a mammal. Also, the prior art and recent studies (see section state of the art) indicate that administration of tamoxifen has increased the risk of stroke and is associated with thrombosis. Accordingly, the subset of patient population who has breast cancer and a cardiovascular indication such as stroke or thrombosis upon administration will have a risk of having stroke or having thrombosis condition. It is known in the art that tamoxifen analogues such as iodotamoxifen or toremifene exhibit similar functional properties like tamoxifen as they are structurally similar. Hence it will be an undue experimentation to one having ordinary skill in the art to find which conditions and which subset of population are suitable for treating with tamoxifen analogues in a method of treating a cardiovascular indication such as stroke, thrombosis and myocardial infarction as claimed. Genetech, 108 F.3d at 1366 states

that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 153, 154, 158, 160-163, 174-176, 181-186 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614) in view of Yang et al. (U.S. 5,219,548, filing date Oct 1 1990).

Barath et al. teaches a method of treating an atherosclerotic blood vessel comprising administering protein kinase c (PKC) inhibitors including tamoxifen (see abstract, col. 6, claims 1, 2). The reference teaches that inhibition of PKC by local

delivery into the vessel wall of specific inhibitors prevents smooth muscle cell proliferation (col. 3, lines 18-20). The reference teaches that the protein kinase C inhibitor agents are useful in reducing the incidence of late restenosis attributed to cellular hyperplasia (abstract).

Thompson et al. teaches that treatment of breast cancer cell lines with tamoxifen results in the rise in TGF-beta1 mRNA expression. The reference in the Materials and Methods section teaches how to measure the level of TGF beta in tamoxifen treated tumors.

The references do not teach administration of tamoxifen analogs in treating a cardiovascular indication like atherosclerosis and does not teach selecting an agent for TGF-beta elevation.

Yang et al. teaches synthesis of iodotamoxifen analogs of tamoxifen and state that the halogenated tamoxifen derivatives possess superior affinities to estrogen receptors (See abstract).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have utilized the methods and materials from Thompson studies to measure the TGF beta level and select agents that elevate the TGF beta level. It would have been obvious to one having ordinary skill in the art from the studies of Thompson that tamoxifen elevated the levels of TGF-beta. Also, it would have been obvious from the studies of Barath et al. that the compound such as Tamoxifen is useful in treating an atherosclerotic condition. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered a structural analog of tamoxifen in a

method of treating a cardiovascular indication such as atherosclerosis because of the prior art teachings of Barath et al. The reference teaches that atherosclerotic blood vessel can be treated by administration of PKC inhibitors including tamoxifen. One having ordinary skill in the art would have been motivated to administer a structural analog of tamoxifen such as 3 or 4-iodotamoxifen taught by Yang et al. because Yang teaches halogenated tamoxifen derivatives possess superior affinities to estrogen receptors. Also, one having ordinary skill in the art would have been motivated to administer a structural analog of tamoxifen such as 3 or 4-iodotamoxifen in expectation of success and in expectation of similar therapeutic benefits. Also, a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. The references do not

explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release, slow release, controlled release, mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations.

Claims 153, 154, 158-163, 174-176, 181-186 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614).in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412)

Barath et al. and Thompson's teachings discussed as above.

The references do not teach administration of tamoxifen analogs in treating a cardiovascular indication like atherosclerosis and does not teach selecting an agent for TGF-beta elevation.

Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen tamoxifen and analogs of tamoxifen, toremifene, droloxifene in vitro (See Abstract).

Warri et al. teach that elevated TGF beta 1 mRNA was observed in vitro and in vivo grown tumor cells treated with toremifene (see Abstract).

One having ordinary skill in the art at the time of the invention would have been motivated to select an analog of tamoxifen agent such as toremifene and administer to inhibit smooth muscle cell proliferation in expectation of success as well in effectively treating atherosclerosis. It would have been obvious to one having ordinary skill in the

art at the time of the invention to have administered a structural analog of tamoxifen in a method of treating a cardiovascular indication such as atherosclerosis because of the prior art teachings of Barath et al. The reference teaches that atherosclerotic blood vessel can be treated by administration of PKC inhibitors including tamoxifen. Also, a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. The references do not teach oral or systemic administrations and the agent is administered in a sustained release form. The references do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration (e.g oral,

systemic) are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412) as applied to claims 153, 154, 158-163, 174-176, 181-186 above and further in view of Cullinan et al. (U.S. 5,457,113).

Barath, Thompson, Warri and Knabbe's teachings discussed as above.

The references do not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent as to inhibit smooth cell proliferation to treat atherosclerosis as taught by Barath et al. because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit smooth cell proliferation to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614 in view of Yang et al. (U.S. 5,219,548, filing date Oct 1 1990) as applied to

claims 153, 154, 158-163, 174-176, 181-186 above and further in view of Cullinan et al. (U.S. 5,457,113).

Barath, Thompson, Yang et al. teachings discussed as above.

The references do not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent as to inhibit smooth cell proliferation to treat atherosclerosis as taught by Barath et al. because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit smooth cell proliferation to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

***Response to Arguments***

(1) ODP rejections:

(i) Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4 of U.S. Patent No. 5,773,479. This rejection is traversed.

Applicants argue that all aspects of the claims need to be considered but not just an aspect in evaluating obviousness type double patenting. In response, claim 1 of the patent '479 is towards a method of treating atherosclerosis comprising administering tamoxifen or an analog of tamoxifen to inhibit or reduce lesion or lipid accumulation.

The instant application teaches the method of treatment of vascular indication selecting an agent for TGF-beta elevation and administering a cytostatic dose of the therapeutic agent such as tamoxifen analog wherein the cardiovascular indication includes atherosclerosis. The patent teaches selection of an agent such as tamoxifen analog. Though it does not explicitly teach the agent is for TGF beta elevation administration of the same compounds in patient will have the same biological effects including TGF-beta elevation. Though the patent do not explicitly teach administration of cytostatic dose, it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. Accordingly, the rejected claims of the instant application is obvious over the claims of the patent.

(II) Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-5 and 9-11 of U.S. Patent No. 5,847,007. This rejection is traversed.

Applicants argue that all aspects of the claims need to be considered but not just an aspect in evaluating obviousness type double patenting. In response, claim 1 of the patent, '007 teaches a method of treatment of atherosclerosis comprising administering a dose of a therapeutic agent in an amount effective to elevate the level of TGF-beta such as tamoxifen or structural analog to inhibit atherosclerotic lesion. The instant application teaches the method of treatment of vascular indication selecting an agent for TGF-beta elevation and administering a cytostatic dose of the therapeutic agent such as tamoxifen analog wherein the cardiovascular indication includes atherosclerosis. The patent teaches selection of an agent such as tamoxifen analog. Though the patent do

not explicitly teach administration of cytostatic dose, it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. Accordingly, the rejected claims of the instant application is obvious over the claims of the patent.

(iii) Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-10 of U.S. Patent No. 6,166,090. This rejection is traversed.

Applicants describe the claims of the patent and state that In contrast, claims of the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta. In response, claim 1 of the patent teaches a method of treating atherosclerosis comprising administering to the mammal an effective amount of a therapeutic agent including tamoxifen or a structural analog to increase the level of TGF-beta, so as to inhibit atherosclerotic lesion. The instant application teaches the method of treatment of vascular indication selecting an agent for TGF-beta elevation and administering a cytostatic dose of the therapeutic agent such as tamoxifen analog wherein the cardiovascular indication includes atherosclerosis. The patent teaches selection of an agent such as tamoxifen analog. Though the patent do not explicitly teach administration of cytostatic dose, it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. Accordingly, the rejected claims of the instant application is obvious over the claims of the patent.

(iv) Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 19, 27, 30-39, and 41-42 of U.S. Patent No. 6,251,920. This rejection is traversed.

Applicants describe the claims of the patent and state that In contrast, claims of the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta. In response, claim 1 of the patent teaches a method of treating a condition selected from stroke, atherosclerosis etc comprising administering to the mammal an effective amount of a therapeutic agent including structural analogs of tamoxifen (e. g toremifene). In claim 33, the patent specifically teaches treating a cardiovascular indication characterized by a lumen diameter comprising administering a cytostatic dose of a therapeutic agent such as toremifene, a structural analog of tamoxifen, wherein the cytostatic dose is effective to increase the level of TGF-beta so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, plaque stability, or any combination thereof. The instant application teaches the method of treatment of vascular indication selecting an agent for TGF-beta elevation and administering a cytostatic dose of the therapeutic agent such as tamoxifen analog wherein the cardiovascular indication includes atherosclerosis. The patent teaches selection of an agent such as tamoxifen analog. Accordingly, the rejected claims of the instant application is obvious over the claims of the patent.

(v) Claims 153-154, 159-160, 165, and 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 6,262,079. This rejection is respectfully traversed.

Applicants describe the claims of the patent and state that In contrast, claims of the present application are directed to methods that select and then administer a cytostatic dose of a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid that elevate TGF-beta. In response, claim 17 of the patent teaches a method of inhibiting smooth muscle cell proliferation comprising administering to a mammal an effective cytostatic antiproliferative amount of a compound selected from the group consisting of tamoxifen, a tamoxifen analog. The instant application teaches the method of treatment of vascular indication selecting an agent for TGF-beta elevation and administering a cytostatic dose of the therapeutic agent such as tamoxifen analog wherein the cardiovascular indication is atherosclerosis, stroke etc, in an amount effective to inhibit smooth muscle cell proliferation. The patent teaches selection of an agent such as tamoxifen analog in smooth muscle cell proliferation inhibition. It would have been obvious to a person of ordinary skill in the art at the time of the invention that administration of the same compounds, tamoxifen analogs to inhibit the smooth cell proliferation would treat a condition such as atheroscleorsis, stroke etc. Though the patent do not explicitly teach administration of cytostatic dose, it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. Accordingly, the rejected claims of the instant application is obvious over the claims of the patent.

(2) 112(1) Enablement Rejection:

Applicants' argue that a compound falling within the scope of the claims that elevates TGF-beta levels would have to be determined or selected, and a cytostatic dose selected or administered does not constitute "undue experimentation," particularly in an art where the level of skill is high and the specification discloses methods to determine agents that elevate TGF-beta levels and thus the claims are enabled. In addition Applicants' have provided literature stating that idoxifene and toremifene have been shown to have beneficial cardiovascular effect.

In response, idoxifene and toremifene are just two analogs of tamoxifen, there are other known and unknown structural analogs of tamoxifen that might or might not be effective in elevating the TGV-beta levels and hence treating all the cardiovascular indications characterized by a decreased lumen diameter. Applicants have shown that raloxifene which has structural relationship to tamoxifen does not elevate TGF-beta levels (see p 3, para 1 of the Rule 132 declaration). Even Applicants' have stated the same in the response to Arguments dated 2/23/2010 - "the Examiner is requested to reconsider that not all structural analogs of tamoxifen elevate TGB-beta (see the Rule 132 Declaration submitted on August 12, 2009). Accordingly, all structural analogs of tamoxifen are not the same and hence it would be an undue experimentation to a person of ordinary skill in the art to determine which compounds would elevate the TGF-beta level and then select the cytostatic dose to treat a cardiovascular indication. Accordingly, the rejection is maintained.

(3) 103(a) rejections:

(i) Applicants' argue that there is no disclosure or suggestion in the Barath et al. patent of an agent that increases the level of TGF-beta, a growth factor and the patent teaches away the use of TGF-beta agent in treating cardiovascular indications. In response, Bharath et al. in claim 1 teaches a method of treating a blood vessel which contains an atherosclerotic lesion comprising administering a protein kinase C inhibitor such as tamoxifen by insertion of a catheter device. Accordingly, the reference teaches treating atherosclerotic lesions comprising administering tamoxifen. Thompson, et al. teaches tamoxifen increases mRNA expression. Accordingly administration of tamoxifen to patients with atherosclerotic lesion would increase the TGF-beta level. Applicants' argue that Bharath's teachings of PKC inhibitors inhibit growth factor transduction (column 4, lines 39-45), e.g., inhibit TGF-beta, thus effectively eliminating or reducing any biological effect induced by the growth factor and thus teach away from the use of TGF-beta elevating agent. Applicant's arguments regarding this have been fully considered. However, it is deemed that Bharath reference does not reach the level of a teaching away from using TGF-beta elevating agent, as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. Bharath teaches that a "series of compounds which act as inhibitors of reactions involved in growth factor signal transduction have been studied with a view to their potential use in tumor chemotherapy. (Int. J. Cancer, 42:382-388 (1988)) and we have unexpectedly discovered that the use of some of these compounds was effective in preventing or

inhibiting restenosis after balloon angioplasty". Bharath's teachings do not state that TGF-beta is inhibited by PKC inhibitors. In fact, Thompson prior art teaches that tamoxifen increases TGF-beta1 mRNA expression in breast cancer cells. The reference merely teaches that the PKC inhibitors are involved in growth factor signal transduction and it would have still been obvious to a person of ordinary skill in the art to have used a tamoxifen analog to treat a cardiovascular indication such as stroke, atherosclerosis etc. because the reference teaches the use of tamoxifen in treating atherosclerotic plaque.

Applicants' argue that it is unclear how the teachings of Thompson et al. and Yang et al. supplement the disclosure in Barath et al. In response, Thompson has been cited to show that tamoxifen increases TGF-beta1 mRNA expression in breast cancer cells and Yang has been cited to show that iodotamoxifen are analogs of tamoxifen and can be synthesized easily. Applicants' argue that Bharath in combination with Thompson and Yang et al. do not teach the instant invention. In response, Bharath teaches tamoxifen is useful in treating atherosclerotic lesions, Thompson teaches that tamoxifen increases mRNA levels, Yang teaches analogs of tamoxifen. It would have obvious to a person of ordinary skill in the art at the time of the invention to have selected and used an agent such as tamoxifen in method of treating cardiovascular indication such as atherosclerosis. It would have been obvious to a person of ordinary skill in the art at the time of the invention to have used a cytostatic dose of the agent in treating a cardiovascular indication because it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. Applicants' state that all structural analogs of tamoxifen do not elevate TGB-beta (see

the Rule 132 Declaration submitted on August 12, 2009) and thus, the combination of the cited art does not provide a reasonable expectation that any particular agent that is structurally related to a compound that elevates TGF-beta would likewise elevate TGF-beta and so be useful to treat similar, much less distinct, indications. In response, iodotamoxifen is structurally very close to tamoxifen than raloxifene to tamoxifen. It would have been obvious to a person of ordinary skill it the art at the time of the invention to have tried using iodotamoxifen in a method of treating a cardiovascular indication.

Applicants' argue that Knabbe et al. and Warri do not supplement what is missing in Barath et al. and Thompson et al. Knabbe and Warri et al. have been cited to show that tamoxifen analogs like toremifene, droloxifene increases TGF-beta. As stated above, Bharath teaches tamoxifen is useful in treating atherosclerotic lesions. It would have obvious to a person of ordinary skill in the art at the time of the invention to have selected and used an agent such as tamoxifen in method of treating cardiovascular indication such as atherosclerosis. It would have been obvious to a person of ordinary skill in the art at the time of the invention to have used a cytostatic dose of the agent in treating a cardiovascular indication because it is within the skill of an ordinary artisan to optimize the dosage amounts of the drug for an effective therapeutic treatment. It would have been obvious to a person of ordinary skill it the art at the time of the invention to have tried using toremifene or droloxifene in a method of treating a cardiovascular indication such as atherosclerosis because they are structural analogs of tamoxifen and

have been shown to increase TGF-beta levels. Accordingly, the rejections are proper and are being maintained.

**Conclusion**

No claims are allowed.

The rejections from the previous office action have been maintained. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627